bilirubinemia in the newborn, as has been suggested.⁵ Finally, practically nothing is known about the influence of diazepam upon the developing fetal brain or the developing neurological functions of the newborn. Thus we do not recommend the subchronic use of diazepam in any stage of pregnancy or in doses higher than 10-20 mg to the mother during labour.—We are, etc.,

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Adverse Reactions to Intra-amniotic Urea and Prostaglandin

SIR,—Since July 1973 it has been our practice to induce mid-trimester therapeutic abortion by the technique of intra-amniotic urea and prostaglandin E₂ injection after amniocentesis, as described by Craft.¹ In the main we have found this method satisfactory, with a minimum of adverse affects. However, we here describe three cases in which adverse reactions, all of a similar nature, occurred at the time of induction of abortion.

The patients, who were 14-16 weeks pregnant, received no premedication and all passed urine within 30 minutes of the start of the procedure. The adverse reaction common to all three cases consisted of rigors, vomiting, severe abdominal pain, and an intense desire to pass urine and defaecate. There was also peripheral vasoconstriction and a rapid, low-volume pulse, with hypotension in one case and peripheral cyanosis in another.

In two cases, in which the liquor was clear, the lower abdominal pain followed immediately after the injection of the urea solution and preceded the injection of 5 mg of prostaglandin. In the third case, in which the liquor was blood-stained, no urea was injected and only 2 mg of prostaglandin by slow injection was used. The first two cases responded, with a return to normal within one hour, to a rapid intravenous infusion of normal saline and intravenous hydrocortisone, diazepam, and promethazine; abortion subsequently occurred. The third patient required an infusion and diazepam alone; abortion did not take place and was induced two weeks later by intra-amniotic hypertonic saline without incident.

The effects of large doses of intravenous prostaglandin are well known, and the features exhibited by the patients described could well represent the effects of a massive dose of prostaglandin introduced into the systemic circulation. This could possibly explain the phenomena in the case in which blood-stained liquor was obtained and one would advise against the use of prostaglandins or urea in such circumstances. However, in the two cases in which the liquor was clear it was more difficult to ascribe the reactions to this cause. These were the cases in which the injection of urea solution caused severe lower abdominal pain. One would therefore advise against the use of prostaglandins when the injection of the urea solution causes lower abdominal pain even though clear liquor was obtained at amniocentesis.

As this series of events has not to our knowledge been previously recorded, we would appreciate any details of similar cases.—We are, etc.,

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¹ Craft, J. L., *Lancet*, 1973, 1, 1344.

CCNU in Treatment of Recurrent Medulloblastoma

SIR,—CCNU is 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea and is one of the nitrosoureas synthesized at the U.S. National Cancer Institute. It has an advantage over 1,3-bis (2-chloroethyl)-3-cyclohexyl-1-nitrosourea (BCNU) in that it can be given by mouth and has a higher lipid solubility. The latter property is probably an important reason why the drug can cross the blood-brain barrier effectively.¹ CCNU has been reported to produce marked improvement in the condition of patients with glioblastoma multiforme² and glioma.³ Hence it seemed reasonable to assess its value in children with recurrent medulloblastoma.

A 7-year-old boy presented in September 1971 with vomiting, headache, nystagmus, papilloedema, and ataxia. Craniotomy and biopsy showed a differentiating medulloblastoma in the cerebellum. Megavoltage radiotherapy was given to the whole central nervous system, the spinal cord receiving 4,000 rads and the brain between 4,600 and 5,400 rads over six weeks, the highest dosage being in the posterior fossa. Subsequently his condition returned to normal apart from minimal ataxia. In December 1972 he developed metastases in the pelvic bones and left femur, the latter proved by biopsy. These were irradiated. Intermittent treatment with cyclophosphamide and vincristine was instituted but later vinblastine was substituted because vincristine caused severe constipation. There was complete relief of pain and the child returned to school. In August 1973, despite perseverance with the above chemotherapy, he developed right facial and ocular muscular palsies. On 4 August 1973 100 mg of CCNU (130 mg/m² body surface area) was given. Three weeks later the ocular palsies were much reduced and six weeks after starting treatment both ocular and facial palsies were barely detectable. Treatment with CCNU was repeated once every six weeks. The child remained well three months after starting treatment, with no depression of the blood count or abnormality of liver function tests.

A 9-year-old girl presented in April 1971 with vomiting, headache, nystagmus, right lateral rectus palsy, and ataxia. Craniotomy and biopsy showed a medulloblastoma in the vermis. Megavoltage radiotherapy was given to the whole central nervous system, the spinal cord receiving 4,000 rads and the brain 4,500 rads over five weeks. Subsequently her condition returned to normal apart from slight past-pointing with the left hand. In May 1972 she developed dysphagia and weakness of the legs. Further megavoltage radiotherapy was given to the posterior fossa, amounting to 2,500 rads over five days, and intermittent treatment with cyclophosphamide and vincristine was started. A month later she was remarkably well and no neurological abnormality could be found. In March 1973 she complained of cramp and slight weakness in the legs, so vinblastine was substituted for vincristine and two months later the weakness was less. On 1 September she suddenly developed severe headache and vomiting and two weeks later she was moribund, with quadriplegia, complete dysphagia, and inability to speak. CCNU 120 mg was given via a nasogastric tube. Ten days later she was able to talk, swallow, and walk with assistance. Treatment with CCNU was repeated six weeks later. Two months after starting treatment she remained well apart from occasional lack of concentration. There was no depression of the blood count or abnormality of liver function tests.

Both these patients showed a remarkable degree of recovery after treatment with CCNU despite the fact that severe deteriora-

tion in their condition had occurred while they were on treatment with cyclophosphamide and vinblastine. This suggests that CCNU is a valuable drug for the treatment of medulloblastoma, though this does not preclude the addition of other drugs such as one of the vinca alkaloids. Furthermore, the simplicity of treatment by a single oral dose every six weeks must favour its use after radiotherapy in the planned initial treatment of medulloblastoma as well as for recurrent disease.

I thank Dr. M. Slavik and the U.S. National Cancer Institute for supplying the CCNU used in this trial.

—I am, etc.,

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Levodopa and Chronic Bronchitis

SIR,—The beneficial effect of levodopa noted by Dr. H. G. Jeffs (9 March, p. 454) has been observed previously,¹ though it is by no means invariable.² One possible mechanism to account for such a bronchodilator action might be through generation of the Schiff base derivative tetrahydropapaveroline,³ which is known to be a β -adrenergic agonist.⁴—I am, etc.,

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SIR,—Dr. H. G. Jeffs's interesting report (9 March, p. 454) of improvement in dyspnoea apparently due to levodopa is consistent with the results of a double-blind study on pulmonary function in patients with Parkinson's disease which showed a significant increase in expiratory flow rates during treatment with levodopa.¹ This was attributed to improvements in motivation and akinesia, but bronchiolar dilation is an attractive additional explanation. However, when levodopa was given to an asthmatic with a drug-induced extrapyramidal syndrome there was a greatly increased frequency of attacks of bronchial asthma.² Clearly, further studies on the actions of levodopa in obstructive airways disease are required. Perhaps other factors such as metabolic effects of levodopa are important in patients with abnormal bronchial secretions.—I am, etc.,

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